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| 10/014,363 | 12/11/2001 | Josef Burg | 20805 | 1126 |
| 151 | 7590 | 02/17/2006 | EXAMINER | |
| HOFFMANN-LA ROCHE INC. PATENT LAW DEPARTMENT 340 KINGSLAND STREET NUTLEY, NJ 07110 | | | SCHNIZER, HOLLY G | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1656 | |

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/014,363

Applicant(s)

BURG ET AL.

Examiner

Holly Schnizer

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 18-23 and 26-30 is/are allowed.
- 6) ☒ Claim(s) 24 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The amendment filed November 25, 2005 has been entered and considered. Claims 1-17 and 31-33 have been cancelled. Therefore, Claims 18-30 are pending.

Rejections Withdrawn

Claim Rejections - 35 USC § 102

The rejection of Claims 1-17 and 31-33 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,583,272 (the '272 patent) is withdrawn in light of the cancellation of these claims.

The rejection of Claims 1-15, and 31-33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 10-14 of U.S. Patent No. 6,583,272 is withdrawn in light of the cancellation of these claims.

The rejection of Claim 16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,583,272 is withdrawn in light of the cancellation of this claim.

Art Unit: 1656

The rejection of Claims 24 and 25 under 35 U.S.C. 102(b) as being anticipated by Bill et al. (Biochim. Biophys. Acta. (1995 Mar) 1261(1): 35-43) is withdrawn in light of the amendment.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bill et al. (Biochim Biophys Acta (1995) 1261: 35-43 (cited in previous Office Action) in view of WO 99/07735 (the '735 publication). Wen et al. (Blood (1993) Vol. 82, No. 5,

pp. 1507-1516) provides evidence that the sequence of wild-type human erythropoietin, used in the Bill et al. reference, is identical to that of claims 24 and 25.

Bill et al. disclose a wild-type human recombinant erythropoietin glycoprotein (human EPO) fused at the N-terminus to a thrombin cleavage site (an N-terminal peptidic extension that is a proteolysis cleavage site) and GST (an N-terminal purification tag) (see p. 36-37, paragraph 2.2; p.37, Fig. 1; p. 38, paragraph 2.4). The erythropoietin disclosed in Bill et al. is wild-type human recombinant erythropoietin and thus has a sequence identical to SEQ ID NO:1. Bill et al. teaches that the EPO gene had been cloned in humans and provides a reference that teaches its cloning and known sequence (p. 35, paragraphs spanning columns and McDonald et al. reference—ref. [2] of Bill et al.). Wen et al., referenced in Bill et al. (see ref. [4] of Bill et al.) provides the sequence of wild-type human erythropoietin which is identical to that of the present claims. Thus, Wen et al. provides evidence that the erythropoietin disclosed in Bill et al. has the sequence of the erythropoietin claimed.

The claims have been amended to limit the proteolytic cleavage site to that selected from APPRIEGR, APP, or APPGAAHY. These sequences, when attached to the N-terminus of erythropoietin form a factor Xa cleavage site (APPRIEGR), an Iga protease cleavage site (APP), and a subtilisin cleavage site (APPGAAHY). Bill et al. discloses a thrombin cleavage site and does not disclose any of these other possible cleavage sites.

However, Bill et al. shows that it was well known in the art to express erythropoietin as a fusion protein with a peptide (GST) that could easily be used to

Art Unit: 1656

purify the protein and that cleavage of the fusion could be accomplished by inserting a protease cleavage site (thrombin) in between the erythropoietin sequence and the GST sequence.

The '735 publication teaches that proteins can be more easily purified if they are expressed with an easily purified fusion partner such as Glutathione-S-transferase (GST) or histidine peptides (His-Tag) (p. 6, last paragraph) and that after elution, the fusion partner can be cleaved off the protein of interest by inserting a protease cleavage site between them such as Subtilisin (or a mutant thereof), factor Xa, thrombin, or IgA protease (p. 7, last paragraph). Thus, the '735 publication provides evidence that GST and Histidine tags are functionally equivalent fusion partners and that thrombin, subtilisin, factor Xa, and IgA protease are functionally equivalent protease cleavage sequences.

Therefore, the Bill et al. and '735 publication references show that various fusion partners including those claimed for easier purification and various protease cleavage sites including those claimed were well known in the art such that it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the expression and purification of erythropoietin by choosing a fusion partner for purification and an optimal protease cleavage site to give the highest expression of the most active erythropoietin product possible. The selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. (MPEP 2144.07; See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945)).

Compliance with the Sequence Rules

Claim 24 fails to comply with the sequence rules. The claim recites amino acid sequences of greater than 4 amino acids. Where the description or claims of a patent application discuss a sequence of 4 or more amino acids, reference must be made to the sequence by use of the sequence identifier preceded by "SEQ ID NO:" in the text of the description or claim even if the sequence is also embedded in the text of the description or claim of the patent application (see 37 C.F.R. 1.821, especially paragraphs (a)-(d)). The examiner did not find these protease cleavage sequences in the present sequence listing. Thus, if Applicants choose to pursue this claim, the examiner suggests amending the claim to read "An erythropoietin glycoprotein comprising the amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5". The sequence of SEQ ID NO:3 appears to be the APPRIEGR-EPO sequence. The sequence of SEQ ID NO:4 appears to be the APP-EPO sequence. The sequence of SEQ ID NO:5 appears to be the APPGAAHY-EPO sequence. Correction is required in response to this Office Action.

Conclusions

Claims 24-25 are rejected. Claims 18-23 and 26-30 are free of the prior art and in condition for allowance for the reasons cited in the previous Office Action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

Art Unit: 1656

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday-Thursday from 10 am to 5:30 pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1656

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Holly Schnizer
February 14, 2006


NASHAAT T. NASHED PHD.
PRIMARY EXAMINER